12.14
Substituent Effects in Electrophilic Aromatic Substitution:
Halogens

F, Cl, Br, and I are ortho-para directing, but deactivating

**Nitration of Chlorobenzene**

\[
\text{Cl} + \text{HNO}_3 + \text{H}_2\text{SO}_4 \rightarrow \text{Cl} + \text{NO}_2 + \text{Cl} + \text{NO}_2 + \text{Cl} + \text{NO}_2 \]

30% 1% 69%

The rate of nitration of chlorobenzene is about 30 times slower than that of benzene.

**Nitration of Toluene vs. Chlorobenzene**

\[
\begin{align*}
\text{CH}_3 & : 42 \quad 2.5 \quad 58 \\
\text{Cl} & : 42 \quad 2.5 \quad 0.029 \quad 0.099 \quad 0.137
\end{align*}
\]

The rate of nitration of chlorobenzene is about 30 times slower than that of benzene.
Table 12.2

Classification of Substituents in Electrophilic Aromatic Substitution Reactions

- Very strongly activating
- Strongly activating
- Activating
- Standard of comparison is H
- Deactivating
- Strongly deactivating
- Very strongly deactivating

Generalizations

1. All activating substituents are ortho-para directors.
2. Halogen substituents are slightly deactivating but ortho-para directing.
3. Strongly deactivating substituents are meta directors.

Electron-Releasing Groups (ERGs) are ortho-para directing and activating

ERG

ERGs include —R, —Ar, and —C=C
Electron-Releasing Groups (ERGs)

ERGs such as —OH, and —OR are strongly activating.

Electron-Releasing Groups (ERGs)

ERGs with a lone pair on the atom directly attached to the ring are ortho-para directing and strongly activating.

Examples

$\text{ERG} = \text{OH, OR, OCR, NH}_2, \text{NHR, NR}_2, \text{NHCR}$

All of these are ortho-para directing and strongly to very strongly activating.
Lone Pair Stabilizes Intermediates for ortho and para Substitution

comparable stabilization not possible for intermediate leading to meta substitution

ERGs Stabilize Intermediates for ortho and para Substitution

Electron-withdrawing Groups (EWGs) Destabilize Intermediates for ortho and para Substitution

—CF₃ is a powerful EWG. It is strongly deactivating and meta directing
Many EWGs Have a Carbonyl Group Attached Directly to the Ring

\[ \text{EWG} = \quad \text{CH} \quad \text{CR} \]
\[ \quad \text{COH} \quad \text{COR} \]
\[ \quad \text{CCI} \]

All of these are meta directing and strongly deactivating.

Other EWGs Include:

\[ \text{EWG} = \quad \text{NO}_2 \]
\[ \quad \text{SO}_3\text{H} \]
\[ \quad \text{C} \equiv \text{N} \]

All of these are meta directing and strongly deactivating.
12.15
Multiple Substituent Effects

The Simplest Case
All possible EAS sites may be equivalent.

Another Straightforward Case
Directing effects of substituents reinforce each other; substitution takes place ortho to the methyl group and meta to the nitro group.
Generalization

Regioselectivity is controlled by the most activating substituent.

Example

Strongly activating substitution occurs ortho to the smaller group.

When activating effects are similar...

Substitution occurs ortho to the smaller group.
Steric effects control regioselectivity when electronic effects are similar.

\[
\begin{align*}
\text{CH}_3 & \quad \text{HNO}_3 \\
\text{H}_2\text{SO}_4 & \quad \text{NO}_2 \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

Position between two substituents is last position to be substituted. 98%.

12.16
Regioselective Synthesis of Disubstituted Aromatic Compounds

Factors to Consider

Order of introduction of substituents to ensure correct orientation.
Which substituent should be introduced first?

If bromine is introduced first, \( p \)-bromoacetophenone is the major product.

Synthesis of \( m \)-Bromoacetophenone
Factors to Consider

- Order of introduction of substituents to ensure correct orientation
- Friedel-Crafts reactions (alkylation, acylation) cannot be carried out on strongly deactivated aromatics

Synthesis of m-Nitroacetophenone

Which substituent should be introduced first?

If NO$_2$ is introduced first, the next step (Friedel-Crafts acylation) fails.
Synthesis of \( m \)-Nitroacetophenone

\[ \text{[Diagram of synthesis process]} \]

Factors to Consider

- Order of introduction of substituents to ensure correct orientation
- Friedel-Crafts reactions (alkylation, acylation) cannot be carried out on strongly deactivated aromatics
- Sometimes electrophilic aromatic substitution must be combined with a functional group transformation

Synthesis of \( p \)-Nitrobenzoic Acid from Toluene

Which first? (oxidation of methyl group or nitration of ring)

\[ \text{[Diagram of synthesis process]} \]
Synthesis of p-Nitrobenzoic Acid from Toluene

CH₃

HNO₃, H₂SO₄, heat

Na₂Cr₂O₇, H₂O, heat

nitration gives m-nitrobenzoic acid

oxidation gives p-nitrobenzoic acid

12.17
Substitution in Naphthalene
two sites possible for electrophilic aromatic substitution
all other sites at which substitution can occur are equivalent to 1 and 2

EAS in Naphthalene

\[
\begin{align*}
\text{Naphthalene} & \\
\text{EAS in Naphthalene} & \\
\text{EAS in Naphthalene} & \\
\end{align*}
\]

is faster at C-1 than at C-2
when attack is at C-1 carbocation is stabilized by allylic resonance benzenoid character of other ring is maintained
EAS in Naphthalene

When attack is at C-2, in order for carbocation to be stabilized by allylic resonance, the benzenoid character of the other ring is sacrificed.

Example: Furan

\[ \text{Furan} + \text{CH}_3\text{COCCH}_3 \xrightarrow{\text{BF}_3} \text{ product } \rightarrow \]

75-92%

Undergoes EAS readily.
C-2 is the most reactive position.